the Kozak consensus sequence, 2) critical factors for the expression of microbial glucanase genes in plants, 3) modifications to the microbial gene needed to permit their expression in plants and are not taught, 4) techniques needed for obtention of introduced plant characteristics and 5) techniques needed to minimize "unpredictability" in this field to avoid undue experimentation.

Not all of these comments appear relevant to the rejected claims which involve various distinct claim types and do not involve the introduction of stable new plant traits. For example, the relevance of the Examiner's comments to the expression cassette (claim 54) and the vector containing the cassette is not seen since they have nothing to do with vector design and construction. It is requested at the outset that the rejection be withdrawn as to claims 54, 55 (vector-containing cassette) and 57 (bacteria-containing vector). There is no assertion that the statements of utility are not credible.

Claim 1 is directed to a method for modifying the carbohydrate composition of a plant or plant organ.[1] Claim 56 is a product-by-process claim directed to a stably transformed, transgenic plant that contains a stably integrated gene encoding a microbial endo-glucanase. Claim 58 is directed to a stably transformed, transgenic plant or plant organ defined in a product-by-process format having a cellular compartment or organelle containing a microbial endo-glucanase modified carbohydrate composition.

The claimed invention, directed to the formation of modified plant carbohydrates in cellar compartments and/or organelles, is described in the specification, as well as how the claimed invention is to be practiced. The measure as to whether the invention is adequately disclosed to permit its practice without undue experimentation or its possession by Applicants is the skilled artisan.

A declaration is enclosed by Dr. J. Pen, one of the inventors and an expert in the field, that addresses points 1-5, raised above. The comments provided by Dr. Pen are incorporated

[1] The process entails growing a transformed transgenic plant containing a vector or recombinant expression construct encoding a microbial endo-glucanase operably linked to a regulatory or leader sequence. The construct causes the glucanase expression and thereby the glucanase modification of the carbohydrate composition contained in a cellular compartment or organelle of the plant. The regulatory sequence is one that directs expression of said enzyme-encoding nucleotide sequence at a selected stage of development or maturity of the transgenic plant or plant organ; one that comprises a 35S CaMV promoter; or one that directs tissue-specific expression of said enzyme-encoding nucleotide sequence in a plant. The leader targets the expressed endo-glucanase to the carbohydrate material in a desired compartment or organelle.

herein. Dr. Pen sets forth his conclusions and supporting rationale. He states that the practice of the present invention would not cause an "undue burden" upon a person skilled in the art and that the trial and error experimentation, to which the Examiner refers, is not specific to the present invention but more accurately relates to the nature of the experimental techniques employed to work the invention and would be accepted by a person skilled in the art as being in the realm of routine experimentation.

Further, it should be noted that representative glucanases are set forth on page 6, starting at line 20. Useful targeting leader sequences are set forth starting at line 25 on page 10. Useful regulatory sequences are set forth starting at line 24 of page 9. Suitable plants are illustrated on page 8 starting at line 25.

The examples, especially Examples 3-5, 7-8, and 11-12 illustrate the operation of the invention in a variety of plants, e g., potato, tomato, tobacco, using various approaches, e.g., agrobacterium, tuber-specific expression construct, and enzymatic modification of carbohydrates at various sites, e.g., leaves, roots and fruit. The specific types of glucanase used are not critical. Their selection is based on the desired end. The known carbohydrase action patterns(s) would aid in the specific selection as would the degree and type branching present in the carbohydrate material. These are the type of selections which would involve at best routine experimentation.

The delivery of the enzymes to a desired site merely involves the selection of a known regulatory element or targeting leader. The elements for doing this are known. The specification, especially the examples, illustrate the operation of the invention. Following, these teachings using conventional materials are not seen to involve undue experimentation, especially as to the claims as amended. The stated object is merely to modify carbohydrate composition of the plant. This does not necessarily require the maintenance of a trait. The nature of the modification, e.g., presence of oligo- and/or monosaccharides, is described as is its monitoring using conventional assays.

Points 1-5 raised by the Examiner in the Official Action do not address the sufficiency of the teachings provided within the specification or their sufficiency in the context of the claimed invention.

Applicants again remind the Examiner that the present application details two examples (Example 2 and Example 9) which illustrate that the expression of two microbial enzymes, α-amylase and glucoamylase, does not require modification of the coding sequence. In the view

that the present claims do not cover the situation where modification of a coding sequence is required, Applicants wholly disagree with the Examiner's requirement that Applicants need to provide details concerning methods for the mutagenesis, modification and alteration of a coding sequence.

In situations where modification of a coding sequence is required, standard techniques would be employed which are well known to those skilled in the relevant art. Applicants acknowledge that genes of microbial origin that require modification of the coding sequence exist, but many genes of microbial origin do not require such modification for efficient plant expression, such genes being readily apparent to persons skilled in the art. Therefore, predictability cannot be said to be at a level that would discourage the skilled practitioner.

Furthermore, Applicants disagree with the Examiner's suggestion that obtaining a transgenic plant with a desirable phenotype is "unpredictable." Note Dr. Pen's declaration, *supra*. The transforming of plants with genes of microbial origin renders the process of obtaining a desirable trait more predictable than the transforming of plants with plant-derived genes. This issue of unpredictability is therefore only applicable to the transforming of plants with plant-derived genes. The unpredictability is due to the close relationship of the plant from which the gene was obtained and the plant into which the gene has been transformed. Interference with the endogenous gene already present in the host plant can therefore be expected. This apparently is not the case when using microbial genes.

The Kossmann *et al.* article, cited by the Examiner in support of his position, has been considered. Its relevance to the claimed invention is not readily apparent. The article published in 1995 makes no mention of the inclusion of microbial endo-glucanases into "transgenic" plants. The enzymes and proteins considered in the reported study are from plant sources. The enzymes include plant ADP-glucose pyrophosphorylase, α-1,4,-glucan synthase and potato "branching" enzyme. Enzymatic starch modification was reported.

In light of the declaration and the arguments provided herein, withdrawal of the rejection is respectfully requested.

CONCLUSION

Having addressed the outstanding objection and rejection, the application is believed to be in condition for allowance and a notice to that effect is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952**, referencing **261922003302**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: June 12, 2000,

Respectfully submitted,

By: _____

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Declaration
in the United States Patent and Trademark Office
In re application of Albert J. J. Van Ooyen *et al.*
Serial No. 09/003,047
Filing date 01/05/98
Art unit 1649
For: Transgenic plants having a modified carbohydrate content

I, Jan Pen, have obtained a PhD in Biochemistry at the University of Groningen (The Netherlands) in 1986. I have been working in plant genetics in various functions at MOGEN International nv. since 1989.

1. The examiner has rejected claims 1, 27 to 28, 42, 48, 51 and 54 to 58 on grounds that these claims allegedly contain "subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention". I will address this issue in my capacity as a person skilled in the art to which this invention pertains.

2. The examiner states that "Applicants claim a method for modifying carbohydrate composition in any transgenic plant or plant organ by stably expressing any expression construct containing any microbial endo-glucanase under a 35S CaMV promoter. However, the specification does not teach those skilled in the art how to identify, characterize and test the nucleotide sequences encompassed by these claims". I submit that identification, characterisation and testing of nucleotide sequences (i.e., microbial endo-glucanases) encompassed by these claims could readily be carried out by a person skilled in the art using known techniques. For example, identification and characterisation of microbial endo-glucanases is not limited to new microbial endo-glucanases, but also covers incorporation of known microbial endo-glucanases in an expression construct. Nevertheless, new microbial endo-glucanases could readily be identified by, for example, sequence homology. Similarly, a person skilled in the art would merely use known techniques in the testing of the relevant nucleotide sequences.

3. The examiner proceeds to state "The specification does not teach if the nucleotide sequence from every microbe is identical, or if all nucleotide sequences of all microbial origin have a common property or physical characteristics". It would be apparent to a skilled person that the nucleotide sequence from every microbe is unlikely to be identical, but would comprise a degree of homology. It would also be apparent that the common property or physical characteristic sought would be the ability to express glucanase under the correct conditions.

4. Then the examiner states that "The specification does not teach those skilled in the art any step on how mutagenesis, modification, the alteration of the coding sequence around the translation initiation site to accommodate Kozak consensus sequence will be performed". The examiner further states that "The instant disclosure fails to teach the factors which are essential for successfully expressing a glucanase gene of microbial origin". All these techniques mentioned by the examiner are merely routine and well known to persons skilled in the art and therefore, it would not have been necessary to have included all these details in the specification. More importantly, the expression of many microbial endo-glucanase would not require modification of the coding sequence and in such situations the above techniques listed by the examiner would be irrelevant. Genes of microbial origin that can profit from modification of the coding sequence

exist, but mostly the genes of microbial origin do not require such modification for basic plant expression and modification of the coding sequence only will further improve expression. Thus, such genes would be readily apparent to persons skilled in the art.

5. The examiner elaborates on the objection concerning modification of the coding sequence, stating that "modification of the coding sequence to enhance the expression of non-plant gene in plants requires many steps which have not been addressed in the instant disclosure which include: changes in localisation of the regions of A+T richness to resemble the plant introns, and the optimisation of the potential plant polyadenylation signal sequences, ATTTA sequences to avoid any destabilisation of the mRNA in the plant". Again, my above comments apply that these modifications will normally improve expression levels obtained through expression of the non-modified genes. In situations where modification of the coding sequence is required, the above mentioned techniques are known to a person skilled in the art and the skilled person would also be able to use them to obtain the desired effect.

6. The examiner then objects that "the process of transforming plants with individual genes to obtain desired phenotypes is unpredictable". I submit that the examiner's opinion is misconceived. The technique of transformation is routine and, at the time of filing the present invention, there were numerous published examples demonstrating the successful transformation of both monocots and dicots. The technique of transformation may be unpredictable to the extent that some plants will not contain the desired gene of interest, however, these plants can readily be identified with the aid of a suitable selection marker. Further, although there are examples where it is shown that it may be possible to obtain a transgenic plant with a transgene which does not express the desired trait, it is submitted that in the case of expression of microbial genes in eukaryotic organisms normally phenotypes are obtained. Use of microbial genes normally will not give rise to rpoduct inhibition in biosynthetic pathways which is the most common reason for the absence of phenotypes in transgenics. Further, in case that nevertheless such a phenomenon may occur, I submit that such transgenic plants will be selectively discarded in preference to plants containing the gene of interest which express the desired trait.

7. In conclusion, I do not believe that the present invention would cause undue burden upon a person skilled in the art. The "trial-and-error" which the examiner refers to is not specific to the present invention, but more accurately relates to the nature of the experimental techniques employed to work the invention and would be accepted by a person skilled in the art as being within the realms of routine experimentation.

The undersigned declares further that all statements of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the instant document and of application Serial No. 09/003,047 or any patents issuing thereon to which the instant document refers.

I. Siden

Dr. Van Pen

June 07, 2000
date